2.04.08 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Summary

Genetic testing is available for both affected individuals, and those at risk for various types of hereditary cancer. This evidence review describes genetic testing for hereditary colorectal cancer (CRC) and polyposis syndromes, including familial adenomatous polyposis (FAP), Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer), MUTYH-associated polyposis (MAP), and Lynch syndrome–related endometrial cancer.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Genetic tests reviewed in this evidence review are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

POLICY STATEMENT

Genetic testing for APC gene mutations may be considered medically necessary in the following patients:

- At-risk relatives (see Policy Guidelines section) of patients with familial adenomatous polyposis (FAP) and/or a known APC mutation.
- Patients with a differential diagnosis of attenuated FAP versus MUTYH-associated polyposis (MAP) versus Lynch syndrome. Whether testing begins with APC mutations or screening for MMR mutations depends on clinical presentation.

Genetic testing for APC gene mutations is not medically necessary for colorectal cancer patients with classical FAP for confirmation of the FAP diagnosis.
2.04.08 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Genetic testing for MUTYH gene mutations may be considered medically necessary in the following patients:
- Patients with a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome and a negative result for APC gene mutations. Family history of no parents or children with FAP is consistent with MAP (autosomal recessive).

Genetic testing for MMR gene mutations may be considered medically necessary in the following patients:
- Patients with colorectal cancer, for the diagnosis of Lynch syndrome (see Policy Guidelines section).
- Patients with endometrial cancer and 1 first-degree relative diagnosed with a Lynch-associated cancer (see Policy Guidelines section), for the diagnosis of Lynch syndrome.
- At-risk relatives (see Policy Guidelines section) of patients with Lynch syndrome with a known MMR mutation.
- Patients with a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome. Whether testing begins with APC mutations or screening for MMR mutations depends on clinical presentation.
- Patients without colorectal cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for MMR mutations.

Genetic testing for EPCAM mutations may be considered medically necessary when any one of the following 3 major criteria (solid bullets) is met:
- Patients with colorectal cancer, for the diagnosis of Lynch syndrome (see Policy Guidelines section) when:
  - Tumor tissue shows lack of MSH2 expression by immunohistochemistry and patient is negative for a germline mutation in MSH2; OR
  - Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline mutation in MSH2, MLH1, PMS2, and MSH6; OR
- At-risk relatives (see Policy Guidelines section) of patients with Lynch syndrome with a known EPCAM mutation; OR
- Patients without colorectal cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for MMR mutations, and when sequencing for MMR mutations is negative.

Genetic testing for BRAF V600E or MLH1 promoter methylation may be considered medically necessary to exclude a diagnosis of Lynch syndrome when the MLH1 protein is not expressed in a colorectal cancer on immunohistochemical analysis.

Pre- and posttest genetic counseling may be considered medically necessary as an adjunct to the genetic testing itself.

Genetic testing for all other gene mutations for Lynch syndrome or colorectal cancer is considered investigational.

POLICY GUIDELINES

Due to the high lifetime risk of cancer of most genetic syndromes discussed in this policy, “at-risk relatives” primarily refers to first-degree relatives. However, some judgment must be allowed, eg, in the case of a small family pedigree, when extended family members may need to be included in the testing
strategy. It is recommended that, when possible, initial genetic testing for familial adenomatous polyposis (FAP) or Lynch syndrome be performed in an affected family member so that testing in unaffected family members can focus on the mutation found in the affected family member (see Benefit Application section).

In many cases, genetic testing for MUTYH gene mutations should first target the specific mutations Y165C and G382D, which account for more than 80% of mutations in white populations, and subsequently proceed to sequencing only as necessary. In other ethnic populations, however, proceeding directly to sequencing is appropriate.

For patients with colorectal cancer being evaluated for Lynch syndrome, either the microsatellite instability (MSI) test, or the immunohistochemical (IHC) test with or without BRAF gene mutation testing, should be used as an initial evaluation of tumor tissue prior to MMR gene analysis. Both tests are not necessary. Proceeding to MMR gene sequencing would depend on results of MSI or IHC testing. IHC testing in particular may help direct which MMR gene likely contains a mutation, if any, and may also provide additional information if MMR genetic testing is inconclusive.

When indicated, genetic sequencing for MMR gene mutations should begin with MLH1 and MSH2 genes, unless otherwise directed by the results of IHC testing. Standard sequencing methods will not detect large deletions or duplications; when MMR gene mutations are expected based on IHC or MSI studies but none are found by standard sequencing, additional testing for large deletions or duplications is appropriate.

Several Clinical Laboratory Improvement Amendments (CLIA)–licensed clinical laboratories offer MMRgene mutation testing for Lynch syndrome. For example, the GeneTests website (available online at:http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/2622?db=genetests) lists 32 U.S.-located laboratories that offer this service. In at least 1 laboratory, Lynch syndrome mutation testing is packaged under 1 copyrighted name. The COLARIS® test (Myriad Genetic Laboratories) includes sequence analysis of MLH1, MSH2, MSH6, and PMS2; large rearrangement analysis for MLH1, MSH2, PMS2, and MSH6 large deletions/duplications; and analysis for large deletions in the EPCAM gene near MSH2. Note that there are 2 versions of this test, the COLARIS (excludes PMS2 testing) and COLARIS Update (includes PMS2 testing). Individualized testing (eg, targeted testing for a family mutation) can also be requested. The COLARIS® PLUS test includes full sequence analysis of MLH1, MSH2, MSH6, PMS2, and MYH genes and rearrangement analysis of MLH1, MSH2, MSH6, MYH, and EPCAM by microarray comparative genomic hybridization analysis, and multiplex ligation-dependent probe amplification analysis for PMS2.

Similarly, GeneTests lists U.S.-based CLIA-licensed clinical laboratories that provide APC mutation testing and those that provide MUTYH mutation testing. The COLARIS® AP test (Myriad Genetic Laboratories) includes DNA sequencing analysis of the APC and MUTYH genes, as well as analysis of large rearrangements in the APC gene not detected by DNA sequencing.

The Amsterdam II Clinical Criteria (all criteria must be fulfilled) are the most stringent criteria for defining families at high risk for Lynch syndrome (Vasen et al. 1999):

- 3 or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter, or renal pelvis);
- 1 should be a first-degree relative of the other 2;
- 2 or more successive generations affected;
- 1 or more relatives diagnosed before the age of 50 years;
- Familial adenomatous polyposis (FAP) should be excluded in cases of colorectal carcinoma;
- Tumors should be verified by pathologic examination.
- Modifications:
  - EITHER: very small families, which cannot be further expanded, can be considered to have hereditary nonpolyposis colorectal cancer (HNPCC) with only 2 colorectal cancers
2.04.08 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

in first degree relatives if at least 2 generations have the cancer and at least 1 case of colorectal cancer was diagnosed by the age of 55 years;

  OR: in families with 2 first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient.

The Revised Bethesda Guidelines (fulfillment of any criterion meets guidelines) are less strict than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families (Umar et al, 2004). The Bethesda guidelines are also considered more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability and/or immunohistochemistry:

- Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50 years old;
- Presence of synchronous or metachronous CRC or other HNPCC–associated tumors,* regardless of age;
- CRC with high microsatellite instability histology diagnosed in a patient less than 60 years old;
- CRC diagnosed in 1 or more first-degree relatives with a Lynch syndrome–associated tumor, with one of the cancers being diagnosed at younger than 50 years of age;
- CRC diagnosed in 2 or more first or second-degree relatives with HNPCC-related tumors,* regardless of age.

* HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain [usually glioblastoma as seen in Turcot syndrome], sebaceous bland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

Summary of Evidence

The evidence for genetic testing for the APC mutations in individuals who have a clinical differential of attenuated familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), and Lynch syndrome, or at-risk relatives of patients with FAP includes a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. For patients with an APC mutation, enhanced surveillance and/or prophylactic treatment will reduce the future incidence of colon cancer and improve health outcomes. A related familial polyposis syndrome, MAP syndrome, is associated with mutations in the MUTYH gene. Testing for this genetic mutation is necessary when the differential diagnosis includes both FAP and MAP, because distinguishing between the 2 leads to different management strategies. Depending on presentation, Lynch syndrome may be part of the same differential diagnosis. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for genetic testing for MMR mutations in (1) individuals who have a clinical differential diagnosis of attenuated FAP, MAP, and Lynch syndrome, or (2) individuals who have colon cancer, or (3) individuals who have endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer, or (4) individuals who are at-risk relatives of patients with Lynch syndrome, or (5) patients without colon cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria includes an Agency for Healthcare Research and Quality report, a supplemental assessment to that report by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, and an EGAPP
recommendation for genetic testing in colorectal cancer (CRC). Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. A chain of indirect evidence from well-designed experimental nonrandomized studies is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known MMR mutation, in that counseling has been shown to influence testing and surveillance choices among unaffected family members of Lynch syndrome patients. One long-term, nonrandomized controlled study and 1 cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed and did not follow recommended colonic surveillance. A positive genetic test for an MMR mutation can also lead to changes in management of other Lynch syndrome malignancies. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for genetic testing for EPCAM mutations in individuals who have CRC in which MMR testing is negative for all MMR mutations but who screen positive for microsatellite instability and lack MSH2 immunohistochemical evidence of protein expression includes mutation prevalence studies and case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Studies have shown an association between EPCAM mutations and Lynch-like disease in families, and the cumulative risk for CRC is similar to carriers of an MSH2 mutation. Identification of an EPCAM mutation could lead to changes in management that improve health outcomes. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for genetic testing for BRAF V600E or MLH1 promoter methylation in individuals who have CRC but in whom MLH1 protein is not expressed on immunohistochemical analysis includes a few case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association of BRAF V600E mutation or MLH1 promoter methylation with sporadic CRC. Therefore, this type of testing could eliminate the need for further genetic testing or counseling for Lynch syndrome. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines for genetic/familial high-risk assessment of colorectal cancer (CRC) recommend 2 approaches to Lynch syndrome mutation screening: (1) all newly diagnosed CRC or (2) all CRC patients diagnosed before age 70 plus those diagnosed at ages 70 and older who meet Bethesda guidelines. Additionally, the guidelines recommend screening for Lynch syndrome in all endometrial cancer patients younger than 50 years. These guidelines note IHC and sometimes MSI testing may be performed at some centers on all newly diagnosed colorectal and endometrial cancer patients to determine need for genetic testing for Lynch syndrome mutations regardless of family history. The guidelines note “evidence has shown 3 deletions in the EPCAM gene, which lead to hypermethylation of the MSH2 promoter and subsequent MSH2 silencing, are an additional cause of Lynch syndrome.” Genetic testing is recommended for at-risk family members of patients with positive mutations in MLH1, MSH2, MSH6, or PMS2. NCCN guidelines also indicate BRAF V600E testing or MLH1 promoter methylation testing may be used when MLH1 is not expressed in the tumor on IHC analysis to exclude a diagnosis of Lynch syndrome. As noted in the NCCN guidelines: “the presence of a BRAF mutation indicates MLH1 expression is downregulated by somatic methylation of the promoter region of the gene and not by germline mutation.” These guidelines also address FAP (classical and attenuated), and MAP, consistent with the information in this evidence review.

NCCN guidelines for colon cancer recommend colon cancer patients 70 years or younger plus those older than 70 years of age who meet the Bethesda guidelines be tested for the MMR protein for possible Lynch syndrome. The colon cancer guidelines also indicate all colon cancer patients should be
questioned about family history and considered for risk assessment as per NCCN colorectal screening guidelines. NCCN guidelines on uterine neoplasms indicate all endometrial cancer patients, especially those younger than 50 years, should be considered for testing for genetic mutations such as Lynch syndrome.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

Under Medicare, genetic tests for cancer are a covered benefit only for a beneficiary with a personal history of an illness, injury, or signs/symptoms thereof (ie, clinically affected). A person with a personal history of a relevant cancer is a clinically affected person, even if the cancer is considered cured. Predictive or presymptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are not covered under national Medicare rules. Centers for Medicare and Medicaid Services (CMS) recognizes Lynch syndrome as "an autosomal dominant syndrome that accounts for about 3% to 5% of colorectal cancer cases. [Lynch] syndrome mutations occur in the following genes: hMLH1, hMSH2, hMSH6, PMS2, and EPCAM." CMS also recognizes FAP and MAP syndromes and their associated mutations.

**REFERENCES**

2.04.08 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

2.04.08 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes


POLFIC HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>March 2012</td>
<td>New Policy</td>
<td>Policy updated with name change and literature review; References 15, 30, 43-49, 52, 53 added. Additional medically necessary indication added for patients with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer.</td>
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<tr>
<td>March 2013</td>
<td>Update policy</td>
<td>Updated with literature review through September 2013. References 24, 33-35 and 58 added. References 39-40 updated. Policy Statement added that BRAF V600E or MLH1 promoter methylation may be considered medically necessary when MLH1 is not expressed in the tumor on IHC analysis.</td>
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<tr>
<td>December 2016</td>
<td>Update Policy</td>
<td>Policy updated with literature review through December 29, 2015; references 59-60 added. Policy statements unchanged.</td>
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